IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Takashi MURAMATSU *et al.*

Title: Early Cancer Tumor Marker

Appl. No.: 10/070,569

Filing Date: March 8, 2002

Examiner: Alana M. HARRIS

Art Unit: 1642

MAIL STOP AF
Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Kenji Kadomatsu do hereby make the following declarations:

1. After obtaining my medical license in 1982, I worked for two years as a Pediatric Surgeon at the Fukuoka Children's Hospital and Kyushu University Hospital in Kyushu, Japan. In 1989, I obtained my Ph.D. from the Kyushu University Graduate School of Medicine. It was during these years of my graduate studies that I discovered a novel growth factor called "Midkine". Ever since this discovery, I have dedicated my research to elucidating the characteristics and functions of Midkine and its potential therapeutic values in various diseases, including cancer. For more details of my educational and professional qualifications, please see my curriculum vitae attached hereto as Exhibit 1.

2. I am a co-author of the Muramatsu *et al.* article published in 1996 in the Journal of Biochemistry, vol. 119, p. 1171-1175 (hereinafter, Muramatsu *et al.*).

3. I have reviewed the above-identified U.S. patent application (U.S. Serial No. 10/070,569 - hereinafter, the '569 application) as originally filed as well as claims 1-9 and 13-16 as amended herewith.

4. I have reviewed the office action of March 9, 2004, particularly the rejection of claims 1, 4, 5, 8, and 9 under 35 USC § 102(b) as being anticipated by Muramatsu *et al.* and the

rejection of claims 1, 4, 5, 8, 9, and 13 under 35 USC § 103(a) as being obvious in view of Muramatsu *et al.*

5. As a co-author of the Muramatsu *et al.* reference, I am quite familiar both with the scope of disclosure and the state of the art at the time of publication. With regard to this Muramatsu *et al.* paper, based on my experiences from the discovery of Midkine to the launching and supervision of further Midkine-related studies, I recognized (i) the importance of this research with regards to forming a basis for the clinical application of midkine, and (ii) provided MBP-MK (a fusion protein of maltose-binding protein and midkine) as a fundamental tool essential to affinity columns for purifying anti-midkine antibodies.

6. It is my understanding that the Examiner believes that, since Muramatsu *et al.* did not disclose that the patients studied suffered from hepatocellular carcinoma that was metastatic, the reference is regarded as disclosing or suggesting a method of detecting "early cancer", i.e., cancer confined to the site of development. However, it is important to note that a cancer that has not metastasized is not necessarily an "early cancer", as that term is defined in the instant specification (i.e., a cancer categorized as stage 0 or stage I of the TNM classification); equally, a cancer that has metastasized is not necessarily an advanced cancer as that term is commonly understood. Accordingly, contrary to the Examiner's suggestion, there is no direct relationship between a cancer not metastasizing and that cancer being an early cancer. In other words, one skilled in the art cannot reasonably predict the stage of a cancer (i.e., stage 0, I, II, III, etc.) based on the presence or absence of metastases alone.

7. Furthermore, upon information and belief, it is my opinion that Muramatsu *et al.* does not contain an inherent or enabling disclosure of the presently claimed invention. Specifically, Muramatsu *et al.* did not classify the experimental samples according to cancer stage because, at the time the experiments described in the reference were conducted, a protein that was secreted into the serum of early cancer patients (i.e., patients categorized at stage 0 or stage I of the TNM classification), and thereby had the potential of becoming a simple and efficient marker for early cancer, was virtually non-existent. Since no one thought that samples derived from early stage cancer patients would yield positive results, no attempt was made to distinguish among cancer stages. Even I, an author of the Muramatsu *et al.* reference, was surprised by the present invention's discovery, that MK is secreted into the serum of early cancer patients and is thereby, an efficient early stage cancer marker that can be simply measured. Thus, even though Muramatsu *et al.* teach that MK levels are increased in the serum of patients with liver cell cancer, it does not necessarily flow that one could predictably use MK for detecting early cancer because, at the time this reference was published, it was the general view that finding markers for early cancer was virtually

impossible.

8. Since, at the time of publication of the Muramatsu *et al.* reference, it was commonly believed that cancer markers were not present in the serum of early cancer patients, those skilled in the prior art would neither have predicted nor expected the positive MK serum samples to have been derived from patients with early cancer. In fact, only by analyzing a number of samples from patients of various early cancers were the present inventors able to conclusively demonstrate that MK is indeed an extremely effective marker for screening and detecting early cancer.

9. In light of the above, it is my opinion that the invention of pending claims 1, 4, 5, 8, 9, and 13 is neither anticipated nor rendered obvious by the Muramatsu *et al.* reference.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: K. Kadomatsu

Kenji Kadomatsu

Dated: September 8, 2004